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New insights and perspectives on the genetics of obsessive-compulsive disorder

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New insights and perspectives on the genetics of obsessive-compulsive disorder

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Psychiatric genetic research has exploded in search of polygenic risk factors over the past decade, but because of the complexity and heterogeneity of mental illnesses, using the current understanding of the genome has not reached the conclusion of finding a cause for psychiatric disorders. Obsessive-compulsive disorder is a relatively common and often debilitating neuropsychiatric disorder that has not been the primary focus in psychiatric research. Clinicians and researchers who have dedicated to investigate the genetics of obsessive-compulsive disorder have detected a strong genetic involvement. This review will provide an update and a new perspective on the current understanding of the genetics of obsessive-compulsive disorder, which includes epidemiological data, family and twins studies, candidate gene studies, genome-wide association studies, copy-number variants, imaging genetics, epigenetics, and gene–environment interaction. *Psychiatr Genet* 29: 142–151 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Obsessive-compulsive disorder (OCD) is a chronic and severe neuropsychiatric disorder, affecting 1–3% of the overall population (Ruscio *et al.*, 2010). It has a lifetime prevalence of 2.3% and 12-month prevalence of 1.2% (Ruscio *et al.*, 2010) in addition to subclinical rates for healthy individuals and individuals with other psychiatric disorders ranging from 13 to 17% and 31 to 49%, respectively (Fullana *et al.*, 2009). OCD is characterized by chronic and often debilitating symptoms of obsessions and compulsions (American Psychiatric Association, 2013). Obsessions are irrational, unwanted, and intrusive thoughts, images, impulses, and urges that generate significant distress, whereas compulsions are repetitive rituals and mental acts that cannot be resisted and are performed in order to alleviate distress (American Psychiatric Association, 2013).

According to the WHO, OCD is one of the top 10 leading causes of disability globally and is the fourth most frequently diagnosed psychiatric disorder. Therefore, improving public awareness in addition to optimizing assessment and treatment is necessary to reduce the societal burden of OCD worldwide.

Keywords: epigenetics, genetics, gene–environment interaction, gene–gene interaction, imaging genetics, obsessive-compulsive disorder, pharmacogenetics

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Treatment of OCD consists of two main streams, psychotherapy and pharmacotherapy. Cognitive behavior therapy (CBT) with exposure and response prevention is the first-line psychological treatment of OCD and serotonergic antidepressants are considered to be the first-line pharmacological treatment of OCD (Koran *et al.*, 2007; Katzman *et al.*, 2014). However, response rate varies ranging from 40 to 60% in medication treatment (McDougall *et al.*, 1993; Foa *et al.*, 2005) and 70 to 86% for CBT (Foa *et al.*, 2005). Furthermore, both treatment options have limitations including side effects from the medications, commitment time, and access for CBT (Sadock *et al.*, 2007). Currently, treatment guideline to differentiate patients according to their response and tolerability to medications and CBT does not exist. Thus, genetic profiling coupled with new knowledge on treatment outcome would provide a substantial leap in the management of OCD.

The underlying etiology of OCD remains largely unknown and improving the understanding of the biological mechanism of OCD will help guide research to optimize the identification of and treatment for this debilitating disease. Genetics has been studied extensively

across psychiatric disorders and experts would agree that the underpinning of psychiatric disorders is at least partly due to polygenic effects.

Traditional genetic studies have utilized hypothesis-driven candidate gene approach. Specific genes were chosen based on the putative biological mechanisms and drug targets of existing psychotropic medications. With advances in genomic technology and bioinformatics, the use of genome-wide association studies (GWAS) has significantly increased in the past decade, which provided ways to investigate previously unexplored regions that may be of great importance in the etiology of OCD.

This review article will first provide an update on the heritability of OCD, followed by results from important human and animal candidate gene studies and GWAS (Burton *et al.*, in press). Subsequently, this article will summarize studies on rare genetic variants, genetics of intermediate phenotypes including drug response and imaging, epigenetics in addition to gene–gene and gene–environment interactions (Burton *et al.*, in press). Finally, this article will end with shared genetic phenomenon: overlap across psychiatric disorders, in light of the Brainstorm paper (Brainstorm *et al.*, 2018), and future perspectives on the genetics of OCD.

Heritability and familiarity of obsessive-compulsive disorder

Family studies have shown that the prevalence of OCD in the relatives of individuals with OCD is higher than the general population, 10–12% versus 1–3%, respectively (Nestadt *et al.*, 2000; Pauls, 2010; Pauls *et al.*, 2014). Twin studies have estimated the heritability of OCD ranging from 42 to 65% (Pauls *et al.*, 2014) for OCD symptoms, 27 to 47% for adult-onset OCD, and 45 to 65% for childhood-onset OCD (van Grootheest *et al.*, 2005; Zilhao *et al.*, 2019).

Candidate gene studies in humans with obsessive-compulsive disorder

Evidence from genetic linkage and candidate gene studies has implicated the importance of several specific regions and genes in the pathoetiology of OCD. The following sections will highlight the major findings from human candidate gene studies of OCD.

Serotonergic system genes

The serotonergic system is one of the most extensively studied systems in the genetics of OCD because of the rationale of using selective serotonin reuptake inhibitors (SSRIs) as the primary pharmacological treatment of OCD based on randomized clinical trials (CPA, 2006; Koran *et al.*, 2007; Soomro *et al.*, 2008; Davis *et al.*, 2013; Murphy *et al.*, 2013; Katzman *et al.*, 2014; Bandelow *et al.*, 2016). The widely known mechanism of action of SSRIs is that they increase the level of serotonin in the

synaptic cleft in order to bind to postsynaptic receptors, which lead to the inhibition of its reuptake into the pre-synaptic cells. The target of SSRIs, the serotonin transporter coded by the *SLC6A4* gene, has consistently been reported to be associated with OCD (Taylor, 2013; Brem *et al.*, 2014; Walitza *et al.*, 2014; Taylor, 2016). These studies have detected the L_A allele of the single nucleotide polymorphism (SNP), rs25531, within the serotonin transporter-linked polymorphic region (5-HTTLPR) of this gene increases the risk for OCD. The serotonin 2A receptor (*HTR2A*) gene is another commonly studied candidate gene for OCD and based on the most recent meta-analysis (Taylor, 2013), it showed a nominally significant result for the rs6311 SNP [odds ratio (OR)=1.219; 95% confidence interval (CI), 1.037–1.433; $P=0.003$]. In addition to the most consistent findings for 5-HTTLPR and *HTR2A* rs6311 in OCD (Sinopoli *et al.*, 2017), mixed results of other serotonergic genes with OCD, including monoamine oxidase A (*MAOA*), tryptophan hydroxylase (*TPH1* and 2), and serotonin 1D-beta receptor (*HTR1B*), have been reported, which require further replication (Walitza *et al.*, 2004; Liu *et al.*, 2013; Taylor, 2013; Brem *et al.*, 2014; Di Nocera *et al.*, 2014; Mas *et al.*, 2014; Sampaio *et al.*, 2015).

Glutamatergic system genes

Evidence has implicated the alteration of the glutamate system as part of the neuropathophysiological etiology of OCD, specifically with a disturbance in the cortico-striato-thalamo-cortical (CSTC) circuit (Pauls *et al.*, 2014). Converging evidence from animal and human studies supports abnormal activation within this circuit, leading to hyperactivation of the orbitofrontal-subcortical pathway, which in turn mediates exaggerated concerns related to danger, harm, symmetry, and contamination, as seen in individuals suffering from OCD (Pauls *et al.*, 2014). Additional rationale of the involvement of the glutamatergic system comes from magnetic resonance spectroscopy (MRS) studies, knock-out mouse models, and clinical trials of glutamatergic agents (Wu *et al.*, 2012). The most studied glutamate gene is the neuronal glutamate transporter (*SLC1A1*) gene and although a general meta-analysis reported a nonsignificant association (Taylor, 2013), an in-depth meta-analysis by Stewart *et al.* (2013s) showed a moderately significant finding for SNPs across the 3' region of the *SLC1A1* gene including rs301443 ($P=0.046$) and rs12682897 ($P=0.012$) when controlled for gender. Dickel *et al.* (2006) also showed an association of rs378041 in *SLC1A1* with early-onset OCD in males, which was replicated by Stewart *et al.* (2007a). Nonetheless, a recent study did not support a role of *SLC1A1* in the risk of OCD (Kim *et al.*, 2018) while others reported positive association in males [rs2228622 (Abdolhosseinzadeh *et al.*, 2019); rs301443 (de Salles Andrade *et al.*, 2019)]. Additional glutamate system genes that have been examined include: the glutamate

receptor, ionotropic N-methyl D-aspartate (NMDA) 2B (*GRIN2B*) gene, which has also been reported to have a significant association with the diagnosis of OCD (Arnold *et al.*, 2004); glutamate related synapse (*SAPAP/DLGAP* family); and NMDA receptor genes (*GRIN* and *GRIK* family) with mixed findings. Although no sex-specific SNP associations were reported, Khramtsova *et al.* (2018) found two significant gene-based associations in the glutamate ionotropic receptor delta type subunit 2 (*GRID2*) and G protein-coupled receptor 135 (*GPR135*) in females but no in males.

Dopaminergic system genes

The dopaminergic system has been examined in OCD due to the effects of antipsychotics as adjunct medications to antidepressants for the treatment of OCD (Pauls *et al.*, 2014). Additional studies using animal models, neuroimaging, and neurochemical approaches also implicate dopaminergic dysfunction in the pathophysiology of OCD (Koo *et al.*, 2010). A meta-analysis (Taylor, 2013) showed a nominally significant finding for the catechol-O-methyltransferase (*COMT*) rs4680 marker (OR = 1.200, $P = 0.010$). *COMT* is involved in the turnover of monoamines in the brain. Five studies found that the low activity *Met* allele of the *COMT* rs4680 (Val158Met) SNP was overrepresented in males with OCD when compared with healthy males (Melo-Felippe *et al.*, 2016). This was later confirmed to be disorder specific in males with OCD when comparing to other psychiatric disorders (Taylor, 2016). Inconsistent findings of the involvement of other dopaminergic system genes suggest that further investigations are warranted in significantly larger and well-characterized samples of OCD.

Other genes

Several additional systems have been investigated in the genetics of OCD and they include the GABAergic system, neurotrophic system, and neuron-related genes. GABA-related genes have been studied with inconsistent and nonreplicated results (Taylor, 2013). Similar lack of support was reported for the brain-derived neurotrophic factor (*BDNF*) gene in OCD including the most studied Val66Met (rs6265) variant (Zai *et al.*, 2015), in addition to genes related to neuroplasticity (Taylor, 2013). A recent study reported an overrepresentation of the *BDNF* rs6265 (Val-66-Met) *Met* allele in healthy individuals when compared with individuals with OCD and this allele was also significantly associated with lower contamination/washing symptom dimension score (Taj *et al.*, 2018). Neuronal growth-related genes including the myelin-oligodendrocyte glycoprotein (*MOG*) (Zai *et al.*, 2004) and oligodendrocyte lineage transcription factor 2 (*OLIG2*) (Stewart *et al.*, 2007b; Zhang *et al.*, 2015b) genes showed promising findings in OCD; however, these associations need to be further confirmed and replicated.

Candidate genes in obsessive-compulsive disorder identified through animal studies

Abnormalities within the CSTC circuitry, which involves the orbitofrontal cortex (OFC), anterior cingulate cortex, and striatum, have been consistently reported in OCD (Saxena and Rauch, 2000; Ting and Feng, 2011; Monteiro and Feng, 2016). Thus, novel animal models of OCD that can manipulate this circuit have been developed and used to further our understanding of the etiology of OCD. Four genetic animal models have been reported: SAP90/PSD95-associated protein 3 (*SAPAP3*) null mice, SLIT and NRTK-like family, member 5 gene (*SLITRK5*) null mice, homeobox B8 (*HOXB8*) null mice, and *SLC1A1/EAAC1* null mice, in addition to a recent multispecies study in OCD.

SAPAP3 encodes a protein, which is highly expressed in the striatum. It is involved in postsynaptic scaffolding at excitatory (glutamatergic) synapses. Welch *et al.* (2007) showed that the *SAPAP* knock-out mice displayed abnormal behaviors consistent with an increase in anxiety and compulsive self-grooming, which were alleviated with repeated administration of fluoxetine. Three human genetic association studies later examined the role of this gene in OCD. Bienvenu *et al.* (2009) tested the association of *SAPAP3* in 383 families with grooming disorders and reported nominally significant association with at least one grooming disorders but not with OCD alone. The second study sequenced *SAPAP3* in patients with trichotillomania and OCD and detected significantly higher percentage of novel non-synonymous heterozygous variants than healthy controls (4.2 versus 1.1%) (Züchner *et al.*, 2009). The third study investigated seven variants within *SAPAP3* in 172 patients with OCD, 45 patients with trichotillomania, and 153 healthy controls (Boardman *et al.*, 2011) and observed a nominal association between rs11583978 and trichotillomania, which did not survive testing for multiple comparison. The authors also detected significant association between earlier age at onset of OCD and the A-T-A-T (rs11583978-rs7541937-rs6662980-rs4652867) haplotype when compared with the C-G-G-G haplotype, implicating this gene in the development of early onset OCD.

SLITRK5 encodes for a protein that regulates neurite outgrowth, which is important in neuronal survival. Shmelkov *et al.* (2010) reported that the *SLITRK5* knock-out mice showed obsessive-compulsive-like behaviors including excessive self-grooming and increased anxiety in the open maze test, which were reversed using chronic fluoxetine treatment. *SLITRK5* is widely expressed in the central nervous system and preferential increase in neuronal activity in the OFC of the *SLITRK5* null mice was observed, which is consistent with human OCD functional imaging findings (Grünblatt *et al.*, 2014).

HOXB8 encodes a nuclear protein that functions as a sequence-specific transcription factor, which has an important role in establishing body patterning during embryonic development. *HOXB8* knockout mice were observed to develop compulsive self-grooming behavior and fur loss in addition to excessive grooming of wildtype (normal) caged-mice (Greer and Capecchi, 2002).

The fourth animal model has shown the greatest genetic contribution in OCD, which is consistent with human genetic findings. The neuronal excitatory amino acid carrier 1 (EAAC1), which is encoded by *SLC1A1*, plays a vital function in transporting glutamate and regulating postsynaptic action of glutamate; it is essential in maintaining extracellular glutamate concentrations below oxidative stress and toxic levels (Aoyama *et al.*, 2006; Scimemi *et al.*, 2009). Thirty percentage of EAAC1 null mice were found to have increased aggression in addition to excessive self-grooming and fur loss (Aoyama *et al.*, 2006), which was reduced with N-acetyl-cysteine treatment, a prodrug of glutathione that modulates the glutamatergic system (Aoyama *et al.*, 2006; Berman *et al.*, 2011).

A recent investigation of 592 cases of OCD and 560 controls that sequenced 608 OCD candidate genes with their regulator elements (Noh *et al.*, 2017) detected genome-wide significance for the neurexin 1 α gene, *NRXN1*, which encodes the synapse cell-adhesion protein, neurexin 1 α , a component of cortico-striatal neural pathway. This study demonstrated the genetic overlap with two animal models of compulsive behavior, in excessive grooming mice, and the so-called canine compulsive behavior. However, the five genes that these investigators found to be most associated with compulsive behavior in mice and dogs, including the well known *SAPAP3* model, were significantly enriched for rare variants in the human sample, but did not reach statistical significance.

Genome-wide association studies

There are four GWASs to date in OCD. The International Obsessive-Compulsive Disorder Foundation Genetics Collaborative (IOCDFGC) conducted the first GWAS (Stewart *et al.*, 2013b), which included 1465 patients with Caucasian OCD, 400 trios, and 5557 controls. For the trio subanalysis, an SNP near the BTB domain containing 3 gene (*BTBD3*) reached genome-wide significance ($P=3.84\times 10^{-8}$). For the case-control subanalysis, several intronic SNPs within the discs large homolog-associated protein 1 (*DLGAP1*), a gene previously found to be associated with OCD, also approached genome-wide significance. However, no genome-wide significant SNPs were identified in the combined trio and case-control analysis. This first GWAS identified top SNPs that were enriched for frontal lobe and methylation expression quantitative trait loci.

The OCD Collaborative Genetics Association Study consortium performed the second GWAS on a sample

of 5061 individuals including 1065 families with 1406 patients with childhood-onset OCD, and unrelated population-based controls (Mattheisen *et al.*, 2015). A marker mapped close to the protein tyrosine phosphatase, receptor type D gene (*PTPRD*) was found to approach genome-wide significance ($P=4.13\times 10^{-7}$), and loci near the cadherin genes, *CDH9* and *CDH10*, were detected to have the next lowest P value ($P=1.76\times 10^{-6}$ and 1.13×10^{-5}).

A recent meta-analysis of the first and second GWASs was published with a total sample of 2688 Caucasian patients with OCD and 7037 ancestry-matched controls (International Obsessive Compulsive Disorder Foundation Genetics and Studies, 2018). Although there was no genome-wide significant markers, the SNPs with the lowest P values tagged the haplotype blocks close to or within the cancer susceptibility 8 (*CASC8/CASC11*), glutamate ionotropic receptor delta type subunit 2 (*GRID2*), and KIT proto-oncogene receptor tyrosine kinase (*KIT*) genes. Previously detected markers in other GWASs have also been detected as top SNPs in this combined GWASs meta-analysis: Ankyrin repeat and SOCS box containing 13 (*ASB13*), *GRIK2*, *CHD20*, *DLGAP1*, fas apoptotic inhibitory molecule 2 (*FAIM2*), *PTPRD*, and R-spondin 4 (*RSPO4*). Gene enrichment analysis conducted from the results of the first two OCD GWASs yielded a molecular landscape that was enriched for proteins involved in synaptic plasticity via regulation of postsynaptic dendritic spine formation through insulin-dependent signalling cascades (van de Vondervoort *et al.*, 2016).

The most recent GWAS analyzed 6931 participants with obsessive-compulsive symptoms (OCS) from The Netherlands Twin Registry (NTR), which identified a genome-wide significant marker (rs8100480) in the BLOC-1 related complex subunit 8 (*BORCS8* or *MEF2BNB*) gene in addition to four significant hits within the myocyte enhancer factor 2B (*MEF2B*) family (den Braber *et al.*, 2016). Polygenic risk score based on the IOCDFGC GWAS significantly predicted OCS, implicating that OCS may potentially be useful in gene discovery for OCD.

Copy number variation in obsessive-compulsive disorder

Other genetic variations including copy number variations (CNVs) using cytogenetic technologies and rare genetic mutation using whole exome or whole genome sequencing techniques should be considered when investigating the underlying genetic risk of OCD.

Microsatellite repeat markers including *SLC6A4* 5-HTTLPR and STin2 VNTR, *BDNF* (GT) $_n$, *DAT1* VNTR, and *DRD4* VNTR have previously been examined in the genetic basis of OCD. A meta-analysis comprising eight datasets examined the 5-HTTLPR marker and reported an overall significant result (mean

OR=1.251; 99th percentile CI, 1.048–1.492; $P=0.001$) (Taylor, 2013). This meta-analysis only investigated biallelic SNPs and thus, multiallelic markers and haplotypes for genetic association with OCD were not included.

To date, several studies have examined CNVs in OCD. Walitza *et al.* (2012) investigated the rs6311 marker in *HTR2A* in 136 pediatric individuals with OCD and a CNV within the *HTR2A* promoter region was significantly associated with the risk for OCD, its onset and severity (Taylor, 2016). A study conducted by the IOCDFGC group (McGrath *et al.*, 2014) did not detect an increase in global CNV burden in OCD but the findings implicated a 3.3-fold increased burden of large deletions on chromosome 16p13.11, a region previously associated with other neurodevelopmental disorders. Another recent study observed a significantly higher frequency of rare CNVs, especially deletions, affecting brain-related genes, in individuals with OCD when compared with healthy controls (Grünblatt *et al.*, 2017). Additional CNV variants that have been detected to date are mostly involved in immune processes and neuronal development (Delorme *et al.*, 2010; Fernandez *et al.*, 2012; Walitza *et al.*, 2012; Nag *et al.*, 2013; Cappi *et al.*, 2014; McGrath *et al.*, 2014; Gazzellone *et al.*, 2016).

A whole exome sequencing study (Cappi *et al.*, 2014) of 20 OCD cases and their unaffected parents detected an increase in de-novo mutation rate relative to the healthy controls from the publicly available 1000 Genomes Project. The mutations identified in the OCD individuals suggested an enrichment of genes involved in immunological systems and the central nervous system.

Pharmacogenetics of antidepressants in obsessive-compulsive disorder

Pharmacogenetics has become increasingly important in the pharmacological treatment of psychiatric disorders because only approximately 50% of patients respond to psychotropic medications in general. Interindividual genetic variations have been the focus of the identification of predictors of drug response and tolerability.

Previous pharmacogenomics studies in OCD reported trends in known genetic variations across the cytochrome P450 liver enzymes, glutamatergic, and serotonergic system genes (Zai *et al.*, 2014).

CYP450 is extensively involved in drug metabolism that plays a central role in medicine. Many medications are not only substrates for these enzymes but may also inhibit or induce enzymatic activity. Genetic variations encoding CYP450 enzymes can lead to alteration of metabolism, which can influence clinical response and adverse events of medications (Elliott *et al.*, 2017). There are many genes coding for CYP450 enzymes that metabolize SSRIs, but only *CYP2D6* and *CYP2C19* have been studied using small sample sizes (Van Nieuwerburgh *et al.*, 2009; Müller *et al.*, 2012; Brandl *et al.*, 2014).

Brandl *et al.* (2014) has reported that individuals with *CYP2D6* nonextensive metabolism (intermediate, poor, and ultrarapid metabolisms) were found to be associated with higher number of antidepressant trials (48 versus 22% with ≥ 4 trials; $P=0.007$) and greater side effects from venlafaxine ($P=0.022$).

Psychotropic medications have pharmacodynamic mechanism of actions, interacting with various neurotransmitter systems including serotonergic, glutamatergic, and dopaminergic systems, which have all been implicated in antidepressant treatment response and adverse effects in OCD (Zai *et al.*, 2014). Serotonergic genes that have been previously examined in OCD include: *SLC6A4* and its promoter (5-HTTLPR), *HTR2A*, *HTR2C*, *HTR1B*, and *TPH*. However, only one study (Correggiari *et al.*, 2012) reported a significant finding between *HTR2A* rs6305 and nonresponders. Real *et al.* (2010) and Zhang *et al.* (2015a) examined the glutamatergic gene *SLC1A1* to prospective SSRI response and reported a significant association with rs301434 and SSRI nonresponse, and between rs301430 and fluoxetine response. A recent study detected significant associations between *SLC1A1* rs2228622 and rs3780413 with fluvoxamine response (Abdolhosseinzadeh *et al.*, 2019). Five studies, investigating the dopaminergic *DRD2*, *DRD4*, *COMT*, and *MAOA*, have been performed, but they were all negative (Zhang *et al.*, 2004; Migueta *et al.*, 2011; Vulink *et al.*, 2012; Viswanath *et al.*, 2013; Umehara *et al.*, 2015) except for *COMT* rs4680 Met/Met genotype with citalopram response (Vulink *et al.*, 2012). Several studies conducted in other candidate genes have detected inconsistent results (Zai *et al.*, 2014). The first pharmacogenetic GWAS of OCD (Qin *et al.*, 2016) was conducted in 804 OCD cases and detected one significant finding with antidepressant response and the *DISP1* rs17162912 SNP ($P=1.76 \times 10^{-8}$); however, this finding was not replicated in an independent OCD sample (Lisoway *et al.*, 2018). Further research is required to clarify the potential roles of these genes in OCD pharmacogenetics.

Endophenotype genetics

The use of endophenotypes as a way to ascertain homogeneous phenotypes for genetic studies has provided important avenue to elucidate the etiology of OCD. The search of endophenotypes in the genetics of OCD has been generally guided by their strong association with OCD, high heritability, and observable similar deficits in unaffected relatives (Gottesman and Gould, 2003; Glahn *et al.*, 2014). Endophenotypes may be of clinical utility in the search for underlying genetic diatheses and thus, for informing diagnostic classification and ultimately providing guidance to treatment management of OCD.

Genetics of cognitive deficits in obsessive-compulsive disorder

Deficits across several cognitive domains with inconsistency have been reported in individuals with OCD. The

observed cognitive deficits in OCD are mainly within the executive function domain (Tükel *et al.*, 2012), cognitive inflexibility (Chamberlain *et al.*, 2006; Bradbury *et al.*, 2011) and motor inhibitory control deficits (Chamberlain *et al.*, 2005). Only three genetic studies to date have examined the effects of genetic vulnerability to these cognitive deficits in OCD (da Rocha *et al.*, 2011; Tükel *et al.*, 2012, 2013). The studies examined a functional genetic variation within *BDNF* and *COMT* in cognitive functions of individuals with OCD. The authors observed poorer performance of the Trail-Making Test (TMT) in OCD *COMT* rs4680 Met carrier, suggesting that the lower activity enzyme with higher level of dopamine in the prefrontal cortex may lead to poorer executive function in patients with OCD (Tükel *et al.*, 2013). Tükel *et al.* (2012) also reported that the *BDNF* rs6265 Met carriers had significantly slower performance on TMT A and B and poorer performance on verbal fluency when compared with healthy control Met carriers (Tükel *et al.*, 2012). The other study showed the *BDNF* rs6265 Met carriers exhibited lower performance on decision making under ambiguous conditions only (da Rocha *et al.*, 2011) but no significant differences in the TMT task performance. Replication studies with larger samples and the development of a broad cognitive battery with systematic and well standardized cognitive tasks that are reliable, easy to interpret, and comparable based on modern cognitive neuroscience approaches will be required in order to derive more definitive conclusions.

Imaging genetics of obsessive-compulsive disorder

Imaging genetics utilizes neuroimaging and genetics to assess the impact of genetic variations on brain function and structure. Recently, large international efforts have begun to use imaging genetics approach on large sample sizes (i.e., ENIGMA, IMAGEN, ADNI, CHARGE) (Medland *et al.*, 2014; Thompson *et al.*, 2014; Bearden and Thompson, 2017; Bogdan *et al.*, 2017). Imaging genetics studies in OCD to date have mainly focused on candidate genes (Arnold *et al.*, 2009a,b; Scherk *et al.*, 2009; Atmaca *et al.*, 2010, 2011; Hesse *et al.*, 2011; Wu *et al.*, 2013; Wolf *et al.*, 2014; Gassó *et al.*, 2015; Mas *et al.*, 2016; Ortiz *et al.*, 2016; Honda *et al.*, 2017). A systematic review (Grünblatt *et al.*, 2014) reported that the main genetic pathways investigated in OCD were among the commonly studied neurotransmitter systems, the serotonergic, glutamatergic, and dopaminergic systems. Within the serotonergic system, the OFC and the raphe nuclei have been found to be associated with the *SLC6A4* 5-HTTLPR gene variant (Grünblatt *et al.*, 2014). A recent study observed a reduction of gray matter volumes in the right frontal pole in OCD L_A allele carriers when compared with healthy controls (Honda *et al.*, 2017). With regard to the glutamatergic system, the CSTC circuit, OFC, thalamus, and anterior cingulate cortex (ACC) have been detected to be associated with several gene variations in glutamate-related

genes (Honda *et al.*, 2017). The increased concentrations of choline measured by ^1H -MRS in the ACC of individuals with OCD have been associated with SNPs in the glutamate receptor AMPA1 gene (*GRI1A1*) (Ortiz *et al.*, 2016). Mean diffusivity in the right anterior and posterior cerebellar lobes has been observed to be associated with the *SLC1A1* rs3087879 marker in patients with OCD (Gassó *et al.*, 2015). Several studies on dopaminergic loci and imaging data have reported a positive association between the dopamine transporter gene (*SLC6A3*) and the metabolism of N-acetylaspartate in the putamen as measured by MRS (Grünblatt *et al.*, 2014), in addition to the mean diffusivity of the white matter in right anterior and posterior cerebellar lobes (Gassó *et al.*, 2015).

Given the complexity and heterogeneity of OCD phenotype, current efforts have been focused on combining polygenic risk scores with neuroimaging, particularly in large consortia, in order to overcome ongoing low statistical power in imaging genetic studies, such as in the ENIGMA consortium (Bearden and Thompson, 2017). Additional techniques including novel biostatistical approaches (Bearden and Thompson, 2017; Bogdan *et al.*, 2017; Mattingsdal *et al.*, 2013; Meda *et al.*, 2012; Nymberg *et al.*, 2013) and machine learning (Mas *et al.*, 2016) have been developed for the prediction of diagnosis, prognosis, and treatment response.

Epigenetics of obsessive-compulsive disorder

Epigenetics refers to the heritable changes in gene expression via DNA methylation or histone modification without changes to the underlying DNA sequence – a change in phenotype without a change in genotype.

In a genome-wide DNA methylation analysis of blood cells from 65 OCD patients and 96 healthy controls, several differentially methylated genes have been identified, which include previously implicated candidate genes for OCD such as *BCYRN1*, *BCOR*, *FGF13*, *HLA-DRB1*, *ARX*, etc. These results further suggest the important role of epigenetic phenomena in the development of OCD (Yue *et al.*, 2016). However, these same findings were not replicated in a smaller study that analyzed 14 candidate genes including *SLC1A1*, *SLC25A12*, *GABBR1*, *GAD1*, *DLGAP1*, *MOG*, *BDNF*, *OLIG2*, *NTRK2*, *NTRK3*, *ESR1*, *SLC6A4*, *TPH2*, and *COMT* (Nissen *et al.*, 2016). Another study observed an increase in the methylation level at the oxytocin receptor (*OXTR*) gene in patients with OCD than in healthy controls and the level of methylation was found to be correlated with OCD symptom severity (Cappi *et al.*, 2016). Grünblatt *et al.* (2018) reported a significantly higher *SLC6A4* DNA methylation levels in pediatric OCD patients when compared with controls and adults with OCD. Cappi *et al.* (2016) observed that individuals with OCD showed more DNA methylation than healthy controls in exons of the oxytocin receptor gene (*OXTR*) using peripheral blood leukocytes.

Gene x gene and gene x environment interactions

The first family study examining gene–gene interaction is the Brazilian collaborative group and they investigated the epistatic effect between *COMT* and *MAOA* in 783 OCD trios (Sampaio *et al.*, 2015), which was negative. Significant gene–gene interactions have been detected between *COMT* rs362204 and two SNPs across the monoamine oxidase B (*MAO-B*) gene, rs1799836 and rs6651806 (McGregor *et al.*, 2016).

Heritability estimates of OCD have detected the importance of specific environmental factors that interact closely with genetic vulnerability, which in turn increase the risk of developing OCD. A population-based study of environmental risk factors for OCD (Brander *et al.*, 2016a) found that impaired fetal growth, preterm birth, breech presentation, Cesarean section, and maternal smoking during pregnancy were associated with the susceptibility of developing OCD (Brander *et al.*, 2016b, 2017). This study also identified a dose-response relationship between the environmental exposures and the development of OCD. The risk modifier for OCD, group A streptococcal infections, have not been consistently demonstrated to date (Hoekstra *et al.*, 2013; Brander *et al.*, 2016a). A recent systematic review has postulated that environmental factors may only increase the OCD risk in genetically susceptible individuals (Brander *et al.*, 2016a).

Shared genetic basis with other psychiatric disorders

Multiple cross-disorder genetic studies have revealed both shared and distinct genetic basis between OCD and several other psychiatric disorders including anorexia nervosa (Yilmaz *et al.*, 2018), autistic spectrum disorder (Guo *et al.*, 2017), attention deficit hyperactivity disorder (Ritter *et al.*, 2017), Tourette disorder (Davis *et al.*, 2013; McGrath *et al.*, 2014; Yu *et al.*, 2015; Zilhão *et al.*, 2016), and schizophrenia (Costas *et al.*, 2016), suggesting common biological mechanism across psychiatric disorders and common genetic markers causing different psychiatric disorders in general. A recent study by the Brainstorm Consortium conducted a collaborative GWAS meta-analysis for 25 brain disorders including psychiatric and neurological disorders in 265 218 cases and 784 632 controls and once again demonstrated significant genetic overlap between several different psychiatric disorders including the first group with anorexia nervosa, OCD, and schizophrenia, and the second group with Tourette disorder, OCD, and major depressive disorder (Brainstorm *et al.*, 2018). These cross-disorder studies support an underlying shared genetic mechanism across various psychiatric disorders including OCD.

Conclusion and future perspective

OCD is a psychiatric syndrome with diverse and heterogeneous symptom characteristics, complex genetics, and neurobiological mechanisms. Individuals with OCD often present with varied symptoms but treatment tends

to be the same, either with the use of an SRI antidepressant, cognitive behavioral therapy, or a combination of both. Management of OCD has not provided tremendous success given its chronic, persisting, and heterogeneous nature. Therefore, improvement in precision medicine may enable clinicians to treat each patient with targeted therapies in the future.

Existing genomic studies have yielded important datasets and interesting findings that will require further exploration, in larger and well-characterized OCD samples. Because of the etiological, neurobiological, and therapeutic heterogeneity and complexity of OCD, it is not surprising that the identification of specific genetic factors has been relatively unproductive thus far. Most robust findings have implicated impairment of the cortico-striatal function and the glutamatergic neurotransmitter system, which have led to preliminary data, supporting the use of glutamatergic agents such as riluzole, memantine, N-acetylcysteine, in the treatment of OCD (Hirschtritt *et al.*, 2017). However, it has been difficult to infer or identify from these results a precise pathophysiological mechanism for OCD or obvious molecular targets for novel treatments. The cause of OCD is likely a combination of common, rare inherited, and de-novo risk variants, suggesting a polygenic model of liability (Browne *et al.*, 2014), in addition to nongenetic factors. Elucidating the genetic underpinnings of this condition has therefore been a major challenge due to the complexity of multifactorial involvements, and will require the integration of genomic, epigenomic, and gene-by-environment information.

In the next several decades, the field of psychiatric genomics will likely expand to involve international collaborative efforts, to use new developments in genetic knowledge (i.e., regulatory elements) and new advances in genetic technology (i.e., high-throughput genomics and biostatistical models), in combination with transcriptomics and proteomics, to gain fresh new insight into the complex genetic architecture of OCD. Understanding the underlying biological mechanisms of OCD will hopefully lead to the introduction of new treatment strategies for this incapacitating psychiatric disorder. New discoveries certainly have the potential to transform the field of psychiatric genetics, which is moving along the goal of eventual translation into clinical practice. These new advances promise new understanding and novel avenues for prevention and treatment of mental illnesses; but they will also present with significant clinical and ethical challenges.

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Conflicts of interest

There are no conflicts of interest.

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